Biologics for Psoriasis: A Translational Research Success Story

Psoriasis is a glowing example of collaboration between clinicians and scientists in an effort to find safe and effective therapies for this debilitating genetic disorder of the skin, joints, and immune system. In some instances, fortuitous clinical observations drove the laboratory work that explained the pathogenesis of this disorder; at other times, therapies were based on findings in the lab. The result has been a dramatic improvement in our understanding of the pathogenesis of this disorder and in our ability to treat psoriatic patients.

Psoriasis was first thought to be a primary disorder of the keratinocyte. In the 1960s, Weinstein, van Scott, and Frost demonstrated abnormal proliferation of keratinocytes in psoriasis (Weinstein and Van Scott, 1965; Weinstein and Frost, 1968). The turnover time of psoriatic epidermis was shown to be markedly faster than that of normal epidermis. Concurrently, van Scott, Auerbach, and Weinstein showed that methotrexate was effective in psoriasis, presumably by targeting those rapidly dividing epidermal cells (Van Scott et al., 1964). Shortly thereafter, Parrish, Fitzpatrick, and colleagues introduced the combination of psoralen and UVA (PUVA) (Melski *et al.*, 1977). PUVA was thought to cross-link DNA strands, and the primary effect was again considered an inhibition of the proliferation of keratinocytes (Lerche *et al.*, 1979). It wasn't until years later that we appreciated the impact of methotrexate and of PUVA on the immune system.

Involvement of the immune system in the pathogenesis of psoriasis was first appreciated as a result of the fortuitous observation that transplant patients who had psoriasis and were treated with cyclosporine exhibited remarkable improvement of their skin disease (Picascia *et al.*, 1988). Griffiths and Voorhees were among the first to point out that cyclosporine's beneficial effect on psoriasis was attributable to the drug's impact on T lymphocytes. With co-workers, they showed that cyclosporine reduces numerous immune cells including T lymphocytes, monocytes, macrophages, and antigen-presenting cells (Griffiths and Voorhees, 1990; Gupta *et al.*, 1989). Working with an illustrious group of scientists, they demonstrated many changes in the immune system from cyclosporine therapy and theorized that upon activation of T cells, lesional T cells released lymphokines that promote keratinocyte proliferation (Baadsgaard *et al.*, 1990).

Independently, Gottlieb and Nickoloff and Griffiths espoused the same point of view, that is, that the T lymphocyte played a critical role in the pathogenesis of psoriasis and was an important target for psoriasis therapies (Gottlieb, 1988; Nickoloff and Griffiths, 1990). The role of the lymphocyte was convincingly confirmed when a group led by James Krueger successfully treated psoriasis using a lymphocyte-selective fusion protein consisting of interleukin-2 and fragments of diphtheria toxin (Gottlieb *et al.*, 1995). The latter compound selectively blocks activated lymphocytes but has no effect on keratinocytes. Eight of 10 patients treated with two doses of this fusion protein had moderate to marked improvement, confirming the role of the lymphocyte.

With attention focused on the T cell, our knowledge about the pathogenesis of psoriasis was now poised to move forward quickly. It was known that activation of T cells requires not only antigen presentation to the T cells, but also costimulation with a number of possible signals. B7 molecules on the surface antigen-presenting cells were shown to provide an important costimulatory signal to their T cell–associated ligands, CD28 and CD152, also known as cytotoxic T lymphocyte–associated antigen-4 (CTLA-4) (Abrams *et al.*, 1999). CTLA-4 Ig, now known as abatacept, is a fusion protein consisting of the Fc portion of human IgG1 fused with the extracellular domain of CTLA-4. By binding to B7 molecules, abatacept prevents the second costimulatory signal, thereby blocking T-cell activation and resulting in improvement in psoriasis (Abrams *et al.*, 1999). Abatacept, approved for the treatment of rheumatoid arthritis, is still

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being studied for psoriasis and psoriatic arthritis.

Soon the concept of a cytokine network in genetically predisposed individuals leading to abnormal keratinocyte proliferation in reaction to infectious or traumatic skin exposures began to emerge. The role of the Th1 cytokine, IFN-γ, was recognized early (Huang *et al.*, 2001). In this cytokine network, activation of lymphocytes and T-cell trafficking were thought to play important roles. Two biologics that were constructed to block T-cell activation, alefacept and efalizumab, were briefly on the market for the treatment of psoriasis. Efalizumab also interfered with T-cell trafficking into inflamed skin (Krueger *et al.*, 2002; Lebwohl et al, 2003).

The role of TNF-α was not appreciated until clinical efficacy had been anecdotally demonstrated (Chamian & Krueger, 2004). After clinical observations that TNF-α antagonists were effective, it was shown that these drugs result in rapid reduction of IL-1 and IL-8 followed by reductions in inflammatory gene expression including IFN-γ, Stat-1, and granzyme B (Gottlieb *et al.*, 2005). The reduction in T-cell activation and decreased production of cytokines, chemokines, and growth factors by lymphocytes, neutrophils, dendritic cells, and keratinocytes stopped the vicious cycle of immune activation leading to keratinocyte proliferation and inflammation.

In the evolving cytokine network leading to psoriasis, Nestle and Conrad pointed out as early as 2004 that p40 was thought to play an important role in psoriasis (Nestle and Conrad, 2004). This led to the development of two antibodies targeting p40, ustekinumab and briakinumab (Lebwohl *et al.*, 2012; Reich *et al.*, 2011). Both biologic agents, which target the p40 components of IL-12 and IL-23, were dramatically effective but because of a small increase in myocardial infarctions in pivotal trials, briakinumab's approval was not pursued.

As our understanding of the cytokine network response to psoriasis evolved, Nickoloff, Nestle, and colleagues pointed out the importance of the IL-23/IL-17 axis (Tonel *et al.*, 2010; Di Cisare *et al.*, 2009). We now know that IL-23 upregulates Th-17 cells to create more IL-17. At least three antibodies targeting IL-17 or its receptor have been studied clinically. The first of these, the recently approved secukinumab, targets IL-17A and has proven to be dramatically effective in the treatment of psoriasis (Langley *et al.*, 2014). Ixekizumab, another antibody to IL-17A, is equally effective, as is brodalumab, an antibody to the IL-17 receptor (Leonardi *et al.*, 2012; Papp *et al.*, 2012).

In conclusion, for the past five decades, advances in our understanding and treatment of psoriasis have resulted from a close collaboration between scientists and clinicians, making psoriasis a model of a disease where basic laboratory scientists and clinicians benefit from interacting with one another. Advances in the laboratory have translated into new therapies that are more targeted, profoundly effective, and safer than older treatments. The next frontier in psoriasis is likely to involve pharmacogenomics or, in the distant future, even gene therapy. We already have a head start thanks to the extensive work identifying psoriasis-associated genes (Gudjonsson *et al.*, 2010; Bowcock *et al.*, 2001; Cargill *et al.*, 2007).

CONFLICT OF INTEREST

Dr. Lebwohl is an investigator for and/or, prior to March 2014, was a paid consultant for AbGenomics, Amgen Canfite Biopharma, Coronado Biosciences, Dermira, Dermipsor, Lilly, Forward Pharma, Janssen Biotech, LEO Pharmaceuticals, Meda, Merck, Novartis, Pfizer, Taro, and UCB Pharma.

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Editor's Note

Since beginning my term as JID Editor in 2012, the importance of unity among the many stakeholders in dermatologic research has become increasingly obvious. The interaction and mutual support of two of these communities—practicing dermatologists and investigators—are especially critical to the future of our specialty. It therefore gives me particular pleasure to see featured in this issue an editorial by the president of the American Academy of Dermatology, the elected representative and spokesperson for more than 10,000 dermatologists as well as one of the foremost clinical investigators and thought leaders in translational research. Dr. Lebwohl beautifully summarizes the advances in basic understanding of the disease psoriasis that have led to progressively targeted and effective therapies within a remarkably short time.

Barbara A. Gilchrest
Editor